ARTICLE

Endoplasmic Reticulum Stress in Skeletal Muscle: Origin and Metabolic Consequences

Louise Deldicque[1], *Peter Hespel*[1], *and Marc Francaux*[2]

[1]Research Centre for Exercise and Health, Department of Biomedical Kinesiology, K.U. Leuven, Leuven, Belgium; and [2]Université catholique de Louvain, Institute of Neuroscience, Louvain-la-Neuve, Belgium

DELDICQUE, L., P. HESPEL, and M. FRANCAUX. Endoplasmic reticulum stress in skeletal muscle: origin and metabolic consequences. *Exerc. Sport Sci. Rev.*, Vol. 40, No. 1, pp. 43–49, 2012. *In secretory organs, such as the liver, the pancreas, and the adipose tissue, endoplasmic reticulum (ER) stress plays a key role in the etiology of cell disturbances implicated in many diseases. Although much less studied, ER stress also is present in skeletal muscle. In the present review, we hypothesize that ER stress may have important metabolic consequences in skeletal muscle. This review presents the situations in which ER stress is activated in skeletal muscle and its metabolic consequences.* **Key Words:** unfolded protein response, XBP1, ATF6, IRE1, exercise, high-fat feeding

INTRODUCTION

Endoplasmic reticulum (ER) stress has been widely studied in pancreatic islets, liver, and adipose tissue where it has been proposed to be involved in the pathogenesis of diabetes (23). Despite the fact that skeletal muscle primarily is responsible for glucose disposal and, therefore, related intimately to disease states like diabetes and obesity, this tissue has been neglected, and much less information exists about ER stress in skeletal muscle in comparison with the other metabolic organs. In addition, although it has a restricted secretory function, skeletal muscle is interesting with respect to the unfolded protein response (UPR) because it contains an extremely extensive network of specialized ER called the *sarcoplasmic reticulum*. Because it is essential to maintain the optimal calcium concentration in the lumen of the sarcoplasmic reticulum for the regulated release of calcium from sarcoplasmic reticulum during contraction in skeletal muscle, any disturbance in the ER could impair muscle contraction.

In skeletal muscle, ER stress first was observed in myopathies, such as myotonic dystrophy Type 1 and sporadic inclusion body myositis. Muscles from myopathic patients displayed larger expressions of chaperones, such as GRP94 and calreticulin, known to be induced by ER stress and to favor muscle regeneration (26). Undoubtedly, ER stress is activated in skeletal muscle in the case of myopathies, but it is unknown if ER stress is triggered in other situations and in healthy skeletal muscle. Recently, it was reported that ER stress markers were not altered in skeletal muscle of ob´/ob´ and high-fat-fed mice compared with controls (18). However, the markers used to support the assertion were not specified in the paper. Based on this report, it generally was accepted that ER stress did not exist in skeletal muscle of high-fat-fed animals. Our group now has published enough evidence to support the existence of ER stress also in nonpathological skeletal muscle. After detailed analysis of the UPR, we clearly showed that ER stress was present in skeletal muscle in high-fat-fed mice (3). In humans, we demonstrated that extreme endurance exercise also activated ER stress and the UPR (8). Because of these findings, we hypothesized that ER stress could have downstream metabolic consequences in skeletal muscle as it does in other organs. The present review will aim at presenting the different situations in which ER stress has been observed in skeletal muscle and the metabolic consequences (see the Table for summary). For the readers who are not familiar with those concepts, ER stress and the UPR will be described in the first section.

ER STRESS AND THE UPR

The ER is an intracellular organelle where folding and posttranslational modifications of proteins occur. Certain conditions, such as high intracellular lipids, glucose deprivation, calcium imbalance, or increased synthesis of secretory proteins, disrupt ER homeostasis and lead to the accumulation of unfolded

Address for correspondence: Louise Deldicque, Tervuursevest 101 Box 1500, 3001 Leuven, Belgium (E-mail: louise.deldicque@faber.kuleuven.be).
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TABLE. Studies having examined the unfolded protein response in skeletal muscle.

	Description	Experimental Model	UPR	Authors
Myopathies	Inclusion body myositis	Human	Yes	Vattemi *et al.*, 2004
	Autoimmune myositis	Human, mouse, C2C12 cells	Yes	Nagaraju *et al.*, 2005
	Inclusion body myositis	Human primary cells	Yes	Nogalska *et al.*, 2006
	Myotonic dystrophy Type I	Human	Yes	Ikezoe *et al.*, 2007
	Juvenile myositis	Mouse	Yes	Li *et al.*, 2009
	Autoimmune myositis	Human	Yes	Vitadello *et al.*, 2010
Nutritional challenge	HFD: 35% fat at weaning, ob^-/ob^-	Mouse	No	Ozcan *et al.*, 2004
	$H6PD^{-/-}$	Mouse	Yes	Lavery *et al.*, 2008
	Glucosamine/high-glucose	L6 cells	Yes	Srinivasan *et al.*, 2009
	Biopsies type II diabetic patients	Human primary cells	Yes	Peter *et al.*, 2009
	Glucosamine	L6 cells, human primary cells	Yes	Raciti *et al.*, 2010
	1-, 2-, or 3-d fasting	Rat	No	Ogata *et al.*, 2010
	HFD: 30% more kcal for 6 wk	Human	No	Deldicque *et al.*, 2010
	HFD-1: 70% fat for 6 wk	Mouse	Yes	Deldicque *et al.*, 2010
	HFD-2: 45% fat for 20 wk	Mouse	Yes	Deldicque *et al.*, 2010
	Palmitic acid	C2C12 cells	Yes	Deldicque *et al.*, 2010
	TUDCA treatment in obese patients	Human	No	Kars *et al.*, 2010
	Palmitic and oleic acid incubation	C2C12 cells	Yes	Peng *et al.*, 2011
	Palmitic and oleic acid perfusion	Mouse	Yes	Peng *et al.*, 2011
Contractile activity	7-d unloading	Rat	No	Hunter *et al.*, 2001
	5 60-min ex bouts	Rat cardiac muscle	No	Murlasits *et al.*, 2007
	2-wk unloading	Rat	No	Ogata *et al.*, 2009
	9-d bed rest	Human	Yes	Alibegovic *et al.*, 2010
	200-km run	Human	Yes	Kim *et al.*, 2011
	Training: 1 $h \cdot d^{-1}$, 5 $d \cdot wk^{-1}$ for 4 wk	Mouse	Yes	Wu *et al.*, 2011
	Test: increasing treadmill exercise to exhaustion			
Development	Myogenesis	C2C12 cells	Yes	Nakanishi *et al.*, 2005
	Myogenesis	C2C12 cells	Yes	Nakanishi *et al.*, 2007
	Aging	Rat	Yes	Ogata *et al.*, 2009

HFD, high-fat diet; H6PD, hexose-6-phosphate dehydrogenase; TUDCA, tauroursodeoxycholic acid; UPR, unfolded protein response.

or misfolded proteins within the ER lumen (30) (Fig. 1). To cope with this stress, cells activate the UPR, a series of events that serve to restore ER function by reducing synthesis of new unfolded and misfolded proteins and by removing those already produced (22). The UPR has three main effectors: activating transcription factor 6 (ATF6), inositol-requiring enzyme 1 alpha (IRE1α), and protein kinase R-like ER protein kinase (PERK). In the basal (inactive) state, each of these factors associates with the chaperone-binding protein/glucose-regulated protein 78 (BiP/GRP78), a member of the heat shock protein 70 (hsp70) family. Upon accumulation of unfolded/misfolded proteins, ATF6, IRE1α, and PERK are released from BiP/GRP78 and become activated. The release of BiP results in oligomerization and activation of the two kinases, PERK and IRE1α, and engages an intricate downstream signaling pathway. Once activated, PERK phosphorylates eukaryotic initiation factor 2 alpha (eIF2α), resulting in general protein translation attenuation. Phosphorylated eIF2α also selectively enhances translation of the activating transcription factor 4 (ATF4). Activated IRE1α after oligomerization and phosphorylation causes splicing of X box–binding protein 1 (XBP1) messenger RNA (mRNA). Translation of spliced XBP1 mRNA produces a transcription factor that upregulates target genes. Activation of the third branch of the UPR requires translocation of ATF6 to the Golgi apparatus where it is cleaved by the serine protease site-1 and the metalloprotease site-2 to produce an active transcription factor. The downstream effects of the UPR are various (attenuation of protein synthesis, upregulation of the expression of chaperones and other proteins that will help restore ER homeostasis, degradation of misfolded and unfolded proteins, triggering of inflammation, and insulin resistance), and the signaling pathways are complex and intricate. For an exhaustive mechanistic explanation, the reader is referred to the reviews on the topic (5,11,23).

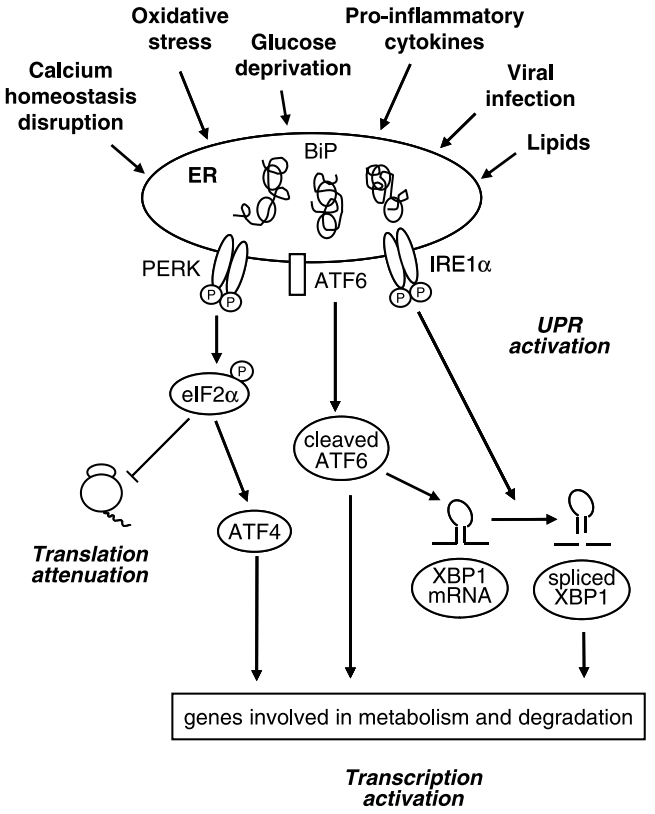

Figure 1. The three branches of the unfolded protein response. ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; BiP, binding protein; eIF2α, eukaryotic initiation factor 2 alpha; ER, endoplasmic reticulum; IRE1α, inositol-requiring enzyme 1 alpha; PERK, protein kinase R-like ER protein kinase; UPR, unfolded protein response; XBP1, X-box binding protein 1.

The initial intent of the UPR is to reestablish homeostasis and adaptative mechanisms predominantly involved in the activation of transcriptional programs that induce expression of genes that are capable of enhancing the protein folding capacity of the ER and genes for ER-assisted degradation (Fig. 2) (9). ER-assisted degradation helps clear the ER of unfolded proteins and export them to the cytosol for degradation. When the UPR fails, the result is cell death, mostly in the form of apoptosis. One key regulator of ER stress-induced cell death is the transcription factor CCAAT/enhancer binding protein homologous protein (CHOP), whose transcription can be upregulated by the PERK-eIF2α-ATF4, the IRE1α-XBP1, and the ATF6 pathways (9). CHOP regulates cell death via several mechanisms, among which, the down-regulation of B-cell leukemia/lymphoma 2 (Bcl-2) expression, resulting in mitochondrial cytochrome c release (9). In addition, IRE1α-apoptosis signal-regulating kinase 1-c-Jun N terminal kinase (JNK) signaling activates the pro-apoptotic Bcl-2 family member BIM, while inhibiting the antiapoptotic protein Bcl-2 (28). IRE1α activation also triggers the recruitment of caspase 12 (caspase 4 in human), a protein with homology to the caspase family of cysteine proteases involved in apoptosis and inflammatory cytokine processing (29).

In addition to apoptosis and protein degradation, ER stress can result in decreased insulin sensitivity (Fig. 3). The decrease in insulin sensitivity mainly is the result of two distinct processes, although additional regulations exist. First, ER stress in pancreatic islets results in dysfunctional beta-cells and in immature insulin release in the blood (23). Second, ER stress in peripheral insulin-sensitive tissues, such as the liver and the adipose tissue, increases JNK-mediated serine phosphorylation of insulin receptor-substrate 1 and thereby inhibits insulin action via decreased signaling to protein kinase B (Akt/PKB) (25).

ER stress also can lead to activation of nuclear factor-kappa B (NF-κB) and inflammation via the three branches of the UPR (5) (Fig. 3). In the first branch, PERK-mediated attenuation of translation results in the release of NF-κB from its inhibitor IκB (inhibitor of NF-κB) because the latter is degraded faster by the proteasome in case of ER stress and thereby less present in the cell. Moreover, PERK signaling will prepare the cell to cope with the generation of reactive oxygen species (ROS) via activation of the nuclear factor erythroid 2-related factor 2. Nrf2 and ATF4 will engage survival responses, coordinate the convergence of ER stress with oxidative stress signaling, and orchestrate the execution of the antioxidant response element-dependent gene transcription program. In the second branch, activated IRE1α recruits tumor necrosis factor α receptor–associated factor 2, and this complex interacts with JNK and IκB kinase and activates them. The third branch of the UPR, the ATF6 pathway, also is known to activate NF-κB.

ER STRESS AND NUTRITIONAL CHALLENGE

The metabolic and nutritional states of the cell are reflected by the levels of selected intermediates (such as cholesterol, fatty acids, or glucose-6-phosphate), as well as by the redox state of the thiol-disulfide and pyridine nucleotide systems. Growing evidence indicates that the ER senses alterations of these factors

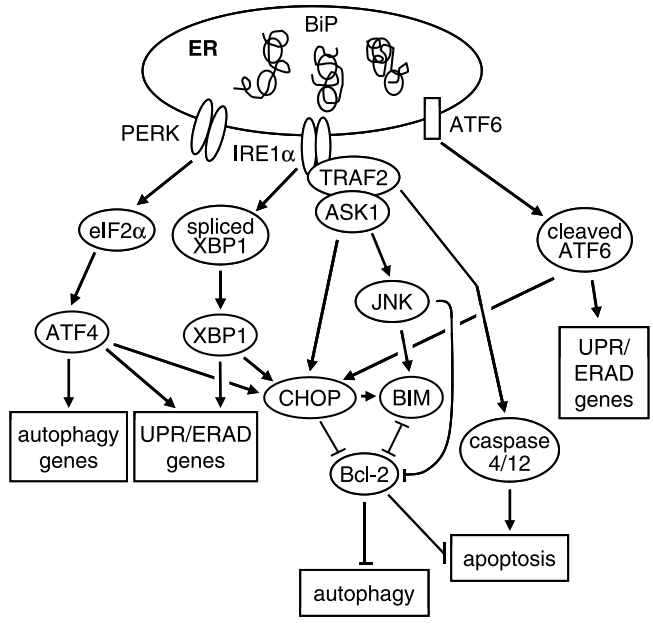

Figure 2. The unfolded protein response and cell death. ASK1, apoptosis signal-regulating kinase 1; Bcl-2, B-cell leukemia/lymphoma 2; CHOP, CCAAT/enhancer binding protein (C/EBP) homologous protein; ERAD, ER-associated degradation; JNK, c-Jun N terminal kinase; TRAF2, tumor necrosis factor-α-receptor-associated factor 2.

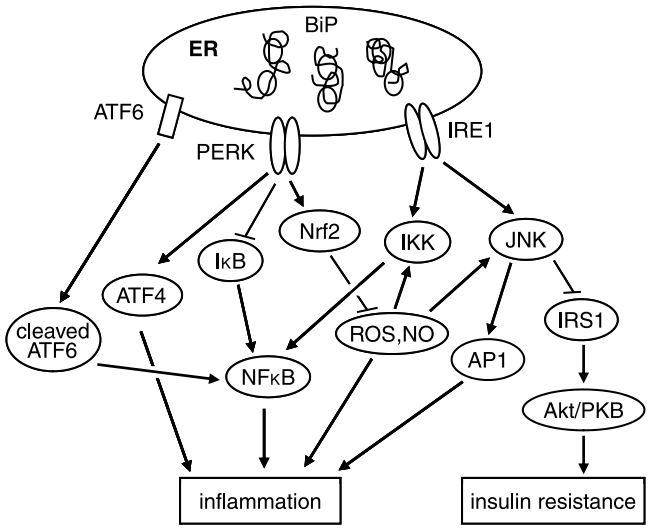

Figure 3. The unfolded protein response, inflammation and insulin resistance. IκB, inhibitor of NF-κB; IRS1, insulin receptor substrate 1; NF-κB, nuclear factor–kappa B; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; ROS; reactive oxygen species.

and, in response, activates the UPR to adjust the metabolic activities to balance intake and requirement (11). It now has become clear that extreme nutritional conditions can trigger the UPR. This includes dietary conditions involving exaggerated supply of either lipids or glucose or the other way around, starvation or glucose deprivation.

We recently showed that ingestion of excessive nutrients, and more specifically lipids, can result in ER stress in skeletal muscle. We tested two different high-fat diet protocols in mice attempting to elicit the UPR. Mice received either a 70% fat diet for 6 wk or 45% fat for 20 wk (3). Although lipid content and duration were different between the two diets, both induced the UPR in muscles. In the same study, using an *in vitro* model where ER stress can be created by addition of pharmacological agents such as tunicamycin or thapsigargin, we found a crosstalk between ER stress and the mammalian target of rapamycin (mTOR) pathway. We hypothesized that this crosstalk could play a role in the ER stress-induced downregulation of protein synthesis in the C2C12 myogenic cell line (3). In a follow-up study (2), ER stress was shown to induce anabolic resistance, which is defined as the inability to increase protein synthesis in response to an increase in amino acids after a meal or other anabolic stimuli. We showed that even low levels of ER stress were sufficient to prevent the activation of mTOR complex 1 (mTORC1) by leucine in C2C12 cells. The inability to activate mTORC1 was not due to a lack of leucine transport but rather to the ER stress-induced decrease in basal PKB phosphorylation resulting in proline-rich Akt substrate of 40 kd (PRAS40) hypophosphorylation and allosteric inhibition of mTORC1. Thus, ER stress was evidenced as one potential mechanism for anabolic resistance and suggested to play a role in the loss of muscle mass during conditions associated with anabolic resistance such as aging, immobilization, and diabetes (2). In agreement with our hypothesis, we showed with those studies that ER stress is activated by high-fat feeding and that ER stress partly is responsible for anabolism resistance in skeletal muscle by downregulating protein synthesis.

Based on data acquired by other groups, it also has become clear that ER stress negatively regulated other metabolic processes such as insulin sensitivity. The PKB/mTOR pathway mediates the response of muscle cells to insulin, and a decreased PKB phosphorylation after insulin stimulation often is used as a marker of insulin resistance. ER stress has been shown to mediate the decrease in insulin-induced PKB phosphorylation after palmitic acid incubation in C2C12 cells and palmitic acid perfusion in rat skeletal muscles (19). The chemical chaperone, 4-phenyl butyric acid, reversed palmitic acid-induced insulin resistance by blocking PERK phosphorylation, ER expansion, and ER stress. Interestingly, the same positive effect on the palmitic acid-reduced PKB phosphorylation was observed after oleic acid addition to palmitic acid. Oleic acid did not affect palmitic acid uptake but generated larger lipid droplets, suggesting that these two fatty acids may differ in their efficiencies to converting fatty acids to neutral lipids to be stored in lipid droplets. All together, those results indicate that ER stress is a key event linking high plasma fatty acid concentration and muscular insulin resistance, thereby supporting our hypothesis linking ER stress and skeletal muscle metabolism regulation.

Insulin resistance is caused not only by high concentration of lipids but also by high concentration of glucose. ER stress has been proposed to mediate glucose-induced insulin resistance as glucose metabolism also occurs in the ER lumen. Indeed, the hexose-6-phosphate dehydrogenase enzyme, which catalyzes the nicotinamide adenine dinucleotide phosphate (NADP)–dependent oxidation of glucose-6-phosphate at the beginning of the pentose phosphate pathway, is localized in the ER. The absence of this enzyme has been shown to impair protein folding because of disruption of the redox balance of the ER and also to activate the UPR pathway and to induce progressive muscle dysfunction in mice, characterized by a shift of Type II to Type I fibers (10).

The hexosamine biosynthetic pathway is a minor glucose metabolic pathway that metabolizes 3% of glucose entering the cell, and the final product of this pathway, uridine diphosphate (UDP)–N-acetyl-glucosamine, as other nucleotide hexosamines, is used in the ER as substrate for protein glycosylation. Although quantitatively using only a minor fraction of glucose, the hexosamine biosynthetic pathway is thought to be an important contributor to the insulin-resistant state. It first was evidenced in L6 skeletal muscle cells, where activation of the hexosamine biosynthetic pathway with glucosamine and high glucose resulted in increased protein expression of ER chaperones (BiP/GRP78, calreticulin, and calnexin) and UDP-N-acetyl-glucosamine, together with impaired insulin-stimulated glucose uptake (24). Conversely, cells silenced for O-glycosyl transferase, a key enzyme of the pathway, showed improved insulin-stimulated glucose uptake. Although cells treated with glucosamine or high glucose showed increased JNK activity, silencing O-glycosyl transferase expression resulted in inhibition of JNK and normalization of glucose uptake (24). Further molecular mechanisms were unraveled after chronic exposure to glucosamine and induction of ER stress in both human and rat myotubes (21). The glucosamine-induced ER stress impaired glucose transporter 4 (GLUT4) production and insulin-induced glucose

uptake via an ATF6-dependent decrease of the GLUT4 regulators myocyte enhancer factor 2A(MEF2A) and peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC1α). Pretreatment of both rat and human myotubes with the chemical chaperones 4-phenylbutyric acid or tauroursodeoxycholic acid completely prevented the effect of glucosamine on both ER stress induction and insulin-induced glucose uptake, evidencing the major involvement of ER stress in glucosamine-induced insulin resistance (21).

The previous studies support our hypothesis and show that protein synthesis and insulin sensitivity are regulated negatively by ER stress in skeletal muscle of mice and myogenic cells. However, does the same mechanism occur in humans? A study in diabetic patients indicated that markers of the UPR were increased in cells isolated from muscle biopsies and cultured in the presence of palmitate (20), suggesting that ER stress likely occurs in human skeletal muscle. In a recent study in our laboratory, healthy subjects were fed a hypercaloric high-fat diet (+30% calories, 50% of total energy intake as fat) for 6 wk (4). Despite an increase in body mass and subcutaneous fat deposits and onset of whole body glucose intolerance as well as an increase in intramyocellular lipid content, we found no change in BiP, PERK, IRE1α, or calnexin expression in the muscle after the dietary intervention. It cannot be excluded that an even longer period of high-fat feeding leading to more severe impairment of muscular insulin sensitivity indeed could have elicited the UPR in skeletal muscles. However, we could not test such dietary intervention because of ethical considerations. In severely obese people with a body mass index (BMI) above 35 and a high degree of insulin resistance, 4 wk of tauroursodeoxycholic acid treatment improved hepatic and muscle insulin sensitivity by approximately 30% compared with a placebo (7). In addition, therapy with tauroursodeoxycholic acid, but not placebo, increased muscle insulin receptor substrate and PKB phosphorylations, and this occurred in the absence of any change in ER stress markers in the muscle. The two later studies indicate that in humans, regulation of insulin sensitivity in skeletal musculature is not linked necessarily with a change in ER stress and/or the UPR. Skeletal muscle seems to face metabolic challenges better than other tissues such as the liver or the adipose tissue. One possible explanation is that skeletal muscle is not a major secretory tissue so that it takes more time to be affected by high-fat feeding, or the insult must be more consequent than in other organs.

To date, only one study has investigated the effect of starvation on ER stress in skeletal muscle of mice (17). CHOP and eIF2α expression were not modified by 1, 2, or 3 d of fasting in the tibialis anterior or soleus muscles, whereas BiP expression decreased only in the tibialis anterior after 2 and 3 d. Because very few markers were analyzed, it is difficult to draw any clear-cut conclusion, and further research will be warranted to determine whether starvation induce ER stress in skeletal muscle.

ER STRESS AND CONTRACTILE ACTIVITY

The release of calcium from the sarcoplasmic reticulum during contraction in skeletal muscle is a highly regulated process; thus, it is essential to maintain the optimal calcium concentration in the lumen. Any disturbance in the ER could impair muscle contraction. In turn, exercise can impair ER and calcium homeostasis. By repeating disturbances in calcium and ER homeostasis, it is likely that exercise training leads to adaptive processes and primes the cell to better face subsequent stress. We thus hypothesized that concomitant treadmill exercise training, by activating the protective UPR, could prevent ER homeostasis disruption induced by a 6-wk high-fat diet in mice (Deldicque *et al.*, unpublished data, 2010). Mice were fed a high-fat diet for 6 wk, and half of them were trained on a treadmill for 60 min, 5 d a week. Compared with control mice receiving normal chow, the high-fat fed mice displayed an increase in several ER stress markers in both tibialis anterior and soleus muscles, and exercise training exacerbated this UPR. Supporting our hypothesis, the potentiation of the UPR and the increase in chaperone content by endurance training might represent a positive adaptation to protect against further cellular stress. The same mechanism of protection was tested in cardiac muscle after ischemia-induced injury (12). The exercise protocol consisted of running at approximately 70% of the maximal oxygen consumption ($\dot{V}O_{2max}$) for 60 min for five consecutive days, after which, ischemia-reperfusion was performed on a few rats from the control and from the trained groups. Although it was clear that training reduced the damage induced by ischemia, this did not occur via increased expression of proteins from the UPR as training did not modify the myocardial expression of CHOP, caspase 12, BiP, GRP94, or calreticulin. Those results show that the UPR temporarily is not the first adaptive mechanism activated to rescue from ischemia-induced injury, but they do not exclude a role for the UPR if training was maintained for a longer period.

We were the first to demonstrate that ER stress is activated in human skeletal muscle after exercise. Three hours after the completion of a 200-km race, the protein expression of BiP and the mRNA level of ATF4 and spliced and unspliced XBP1 were increased compared with basal levels (8). At the same time, the amount of ubiquitin-conjugated proteins and the chymotrypsin-like activity of the proteasome were decreased, whereas the mRNA level of the ubiquitin ligases, muscle-specific RING finger 1, and muscle atrophy F box were increased. As inflammation and oxidative stress were activated in skeletal muscle after the race, the increase in the UPR and the reduced activity of the proteasome could be compensatory mechanisms to cope with cellular stress.

In general, our data suggest that the activation of the UPR after exercise is a protective mechanism against current and future stress. This idea is corroborated by a very recent study in mice (27). A single moderate-intensity exercise bout activated the UPR in skeletal muscle of mice, whereas the activation was less or even repressed for some markers after several training sessions. These results suggest that moderate exercise and the accompanying physiological ER stress in skeletal muscle may lead to adaptation and protect skeletal muscle against further stress. It is of note that the UPR similarly was activated in different muscles from the limb (quadriceps and gastrocnemius), whereas it largely was unaffected in non-weight-bearing back muscle (erector spinae) or in the heart. This implies that mechanical stress exerted by muscle contraction and/or local metabolic changes in the muscle that directly are involved in exercise play a

major role in the activation of the UPR. It was found that PGC-1α was one of the key factors in the regulation of the UPR through coactivation of ATF6α (27).

What happens if muscle contractile activity is inhibited by unloading? Following the same premise as for exercise, any disruption in ER homeostasis will induce the UPR, and this should hold true for unloading. Compared with rats allowed to move normally, rats subjected to unloading for 7 d (6) or for 2 wk (16) did not display a clear pattern of ER stress despite muscle atrophy. In humans, a microarray analysis performed on biopsies during a bed rest campaign revealed that several genes induced by the UPR and genes involved in insulin resistance were upregulated in the skeletal muscle after 9 d (1). Because of a lack of data, further research will be needed to conclude on the effect of unloading on ER stress in skeletal muscle.

ER STRESS AND DEVELOPMENT

Skeletal muscle development involves the fusion of myoblasts to form multinucleated cells, myotubes, which eventually differentiate into myofibers. Myoblast cells begin to exhibit considerable morphological changes when cultures are switched to low concentrations of mitogens. During this process, myoblasts express muscle-specific proteins and fuse into multinucleated myotubes, meanwhile caspase-3 and apoptosis are activated. Caspase-3 likely is to be activated partially by caspase-12 as the latter has been shown to be activated extensively in differentiating myoblasts *in vivo* and *in vitro* (15). Differentiating myoblasts showed induction of two other ER stress-specific proteins, CHOP and BiP, via activation of ATF6. The repression of ATF6 activation blocked apoptosis and myotube formation (15). Those results indicate that the UPR is required during myogenesis. Even more, treating C2C12 myoblasts with the ER stress inducers tunicamycin and thapsigargin enhanced apoptosis during myoblast fusion, and surviving cells were highly resistant to the apoptotic stimuli (14). The surviving cells efficiently formed contracting myofibers that are otherwise rarely found in culture systems of myoblast cell lines. Efficient myofiber formation is of great interest from a therapeutic point of view because it is important for enhancing muscle growth after injury or decreasing the loss of muscle mass because of disease or aging.

With age, many of the key components of the UPR, such as the chaperones and enzymes, display reduced expression and activity resulting in a dysfunctional ER (13). ER stress has been implicated in many aging-related neurodegenerative diseases, such as Alzheimer, amyotrophic lateral sclerosis, and Parkinson, but does it specifically impact skeletal muscle during aging? In 32-month-old rats, expression of specific chaperones such as Erp29, hsp70, and calreticulin in the skeletal muscle was decreased compared with that in 6-month-old rats, whereas, at the same time, ER stress and apoptosis markers were increased (16). One could postulate that the reduced content in chaperones observed with aging will favor the development of cellular stress. Consequently, the following question arises but remains unanswered: can skeletal muscle in the elderly be preserved from ER stress by increasing chaperones content through increased physical activity? This will be worth to be tested.

CONCLUSIONS

The present review focused on the existence of ER stress and the UPR in skeletal muscle. We hypothesized that ER stress may have important metabolic consequences in this organ, and we presented evidence that ER stress can downregulate protein synthesis and favor insulin resistance. Despite its limited role in protein secretion, skeletal muscle contains an extremely extensive network of specialized ER called the *sarcoplasmic reticulum*. Maintaining the optimal calcium concentration in the sarcoplasmic reticulum lumen is critical to regulating sarcoplasmic reticulum calcium release in the skeletal muscle during contractions. Homeostasis of the ER is not only critical to muscle contraction but also important to maintaining optimal activation of the PKB pathway, which can be inhibited by ER stress. Impairment in PKB activation can lead to anabolic and insulin resistance. With the skeletal muscle being the biggest glucose consuming tissue, it is of utmost importance to keep the ER in minimal stress conditions. We further hypothesize that increasing ER chaperones by exercise training could be an effective strategy for achieving this purpose.

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